9th January 1967.

Dr H. Gobind Khorana,
University of Wisconsin,
Institute for Enzyme Research,
1710 University Avenue,
Madison, Wisconsin 53706,
U.S.A.

Dear Gobind,

Very pleased to get your letter of 3rd January. Brian Clark tells me that he has not tested GUA to see whether it binds formylmethionine, but he will try to do so in the near future. We are slightly worried, however, in case the effect could be due to a small number of molecules of your Poly GUA which have an incorrect sequence and begin with GUG. Have you any means of testing this?

I have been thinking what new evidence we need in order to establish the Adaptor Hypothesis, or at any rate the pairing rules predicted by it. It is very satisfactory that a G in the anticodon of your phenylalanine tRNA recognizes both U and C in the third position of the codon. Obviously the next thing is to try and show that both A and G in the third position of the codon are recognized by U on the anticodon. This would mean trying to find the anticodon for, say, lysine or glutamic acid. There is not much doubt in my mind that that is how things will turn out. In any case I shall try to persuade someone here to do this.

I am more worried about the triplets recognized by I in the anticodon. Of course your binding studies for alanine show that in the third position of the codon U, C and A are recognized and G is either recognized only slightly or not at all. This latter point is in fact the crucial question. Can I recognize a G in the third position? To be sure of this one should really try to use synthesis, not binding. Sydney pointed out to me that valine is very favourable for this since you already have messengers which code

for GUU, GUA and GUG. The great problem is whether the tRNA's for valine can be separated, and in particular whether one can be sure that no minor component is present. Various rather complicated experiments, using both binding and synthesis, suggest themselves but perhaps we had better discuss these at La Jolla.

Another approach is to try to find the codon for isoleucine. Again the problem may be that there may be a major component that recognizes AUU and AUC and in addition a minor tRNA which recognizes both these triplets and also AUA. Nevertheless we have been wondering whether it would be worthwhile to try to find the distribution of Inosine in a fractionation of the tRNA from E. coli, as there is so little I in the tRNA as a whole from this species. It would certainly be interesting if the I was correlated with isoleucine-accepting activity.

I have not heard from Leslie Orgel yet about Yanofsky but perhaps I shall hear in the next few days. There have been no further significant developments here. You may be amused to learn that when I went to see Pelc's models showing how amino acids could be fitted to codons I found that he had built them all backwards. His so called AAG, for example, was actually GAA. There were lots of other things wrong with the models but we need hardly worry about them after such a bloomer.

It will be wonderful to see you at La Jolla. I shall probably arrive about a day before you but I hope that my internal clock will be adjusted by then.

F.H.C. Crick.